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(71) Applicant and

(72) Inventor: **HOGAN, Kirk [US/US];** 3417 Crestwood Drive, Madison, WI 53705 (US).

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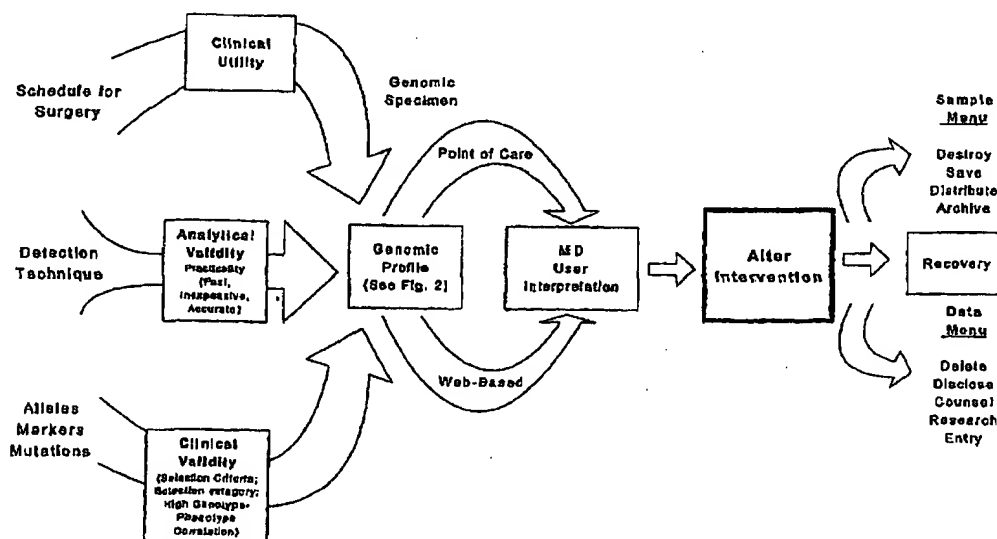
(74) Agents: **CASIMIR, David, A. et al.;** Medlen & Carroll, LLP, 101 Howard Street, Suite 350, San Francisco, CA 94105 (US).

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(54) Title: **METHODS AND COMPOSITIONS FOR PERIOPERATIVE GENOMIC PROFILING**

(57) Abstract: The present invention relates to methods for perioperative genomic screening of subjects, in particular to perioperative screening for markers indicative of responses to anesthesia and other perioperative or operative treatments and procedures. The present invention also provides compositions for use in screening methods. The methods and compositions of the present invention find use in tailoring a subject's medical or surgical treatment to reflect genetic information that predicts a subject's response to medications or techniques used in the procedure.

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INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

Biosis, EPO-Internal, MEDLINE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 413 907 A (WORTON RONALD G ET AL) 9 May 1995 (1995-05-09) column 1, line 1 - column 3, line 56	1-20
A	WO 99 44062 A (SAUTER GUIDO; US HEALTH (US); KONONEN JUHA (US); KALLIONIEMI OLLI) 2 September 1999 (1999-09-02) abstract	1-20

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

30 January 2003

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stachowiak, O

INTERNATIONAL SEARCH REPORT

 Inte 1st Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>TANAKA T ET AL: "PROGNOSTIC DISCRIMINATION AMONG NEUROBLASTOMAS ACCORDING TO HA-RAS/TRK A GENE EXPRESSION A COMPARISON OF THE PROFILES OF NEUROBLASTOMAS DETECTED CLINICALLY AND THOSE DETECTED THROUGH MASS SCREENING" CANCER, AMERICAN CANCER SOCIETY, PHILADELPHIA, PA, US, vol. 83, no. 8, 15 October 1998 (1998-10-15), pages 1626-1633, XP001027462 ISSN: 0008-543X the whole document</p> <p>---</p>	1-20
A	<p>LOWE S ET AL: "Anesthetic implications of the child with homocystinuria." JOURNAL OF CLINICAL ANESTHESIA. UNITED STATES 1994 MAR-APR, vol. 6, no. 2, March 1994 (1994-03), pages 142-144, XP001120069 ISSN: 0952-8180 page 142, column 2, paragraph 1 -page 143, column 1, paragraph 4</p> <p>---</p>	1-20
A	<p>SCHORGE JOHN O ET AL: "Clinically significant venous thromboembolism after gynecologic surgery." JOURNAL OF REPRODUCTIVE MEDICINE, vol. 44, no. 8, August 1999 (1999-08), pages 669-673, XP001120049 ISSN: 0024-7758 the whole document</p> <p>---</p>	1-20
A	<p>BADNER NEAL H ET AL: "The use of intraoperative nitrous oxide leads to postoperative increases in plasma homocysteine." ANESTHESIA & ANALGESIA, vol. 87, no. 3, 1998, pages 711-713, XP009000817 ISSN: 0003-2999 abstract</p> <p>---</p>	1-20
A	<p>FRITZE J ET AL: "HORIZONTAL-TWO-DIMENSIONAL ELECTROPHORESIS OF PLASMA BUTYRYLCHOLINESTERASE" BIOLOGICAL CHEMISTRY HOPPE-SEYLER, vol. 368, no. 3, 1987, pages 295-298, XP009000749 ISSN: 0177-3593 abstract</p> <p>---</p>	1-20
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INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/US 01/41331

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MONNIER NICOLE ET AL: "Malignant-hyperthermia susceptibility is associated with a mutation of the alpha-1-subunit of the human dihydropyridine-sensitive L-type voltage-dependent calcium-channel receptor in skeletal muscle." AMERICAN JOURNAL OF HUMAN GENETICS, vol. 60, no. 6, 1997, pages 1316-1325, XP009004568 ISSN: 0002-9297 cited in the application the whole document</p>	1-20
A	<p>BRANDT ANNEBILL ET AL: "Screening of the ryanodine receptor gene in 105 malignant hyperthermia families: Novel mutations and concordance with the in vitro contracture test." HUMAN MOLECULAR GENETICS, vol. 8, no. 11, October 1999 (1999-10), pages 2055-2062, XP001135004 ISSN: 0964-6906 cited in the application abstract</p>	1-20
A	<p>TSAI M Y ET AL: "HIGH PREVALENCE OF A MUTATION IN THE CYSTATHIONINE BETA-SYNTHASE GENE" AMERICAN JOURNAL OF HUMAN GENETICS, UNIVERSITY OF CHICAGO PRESS, CHICAGO,, US, vol. 59, no. 6, 1 December 1996 (1996-12-01), pages 1262-1267, XP000672710 ISSN: 0002-9297 cited in the application abstract</p>	1-20
A	<p>HARMON DAWN L ET AL: "Methionine synthase D919G polymorphism is a significant but modest determinant of circulating homocysteine concentrations." GENETIC EPIDEMIOLOGY, vol. 17, no. 4, November 1999 (1999-11), pages 298-309, XP009004569 ISSN: 0741-0395 cited in the application the whole document</p>	1-20

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INTERNATIONAL SEARCH REPORT

Inte 1al Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>FROSST P ET AL: "A CANDIDATE GENETIC RISK FACTOR FOR VASCULAR DISEASE: A COMMON MUTATION IN METHYLENETETRAHYDROFOLATE REDUCTASE" NATURE GENETICS, NEW YORK, NY, US, vol. 10, no. 1, 1 May 1995 (1995-05-01), pages 111-113, XP000198175 ISSN: 1061-4036 cited in the application the whole document</p> <p>---</p>	1-20
A	<p>SACHSE CHRISTOPH ET AL: "Cytochrome P450 2D6 variants in a Caucasian population: Allele frequencies and phenotypic consequences." AMERICAN JOURNAL OF HUMAN GENETICS, vol. 60, no. 2, 1997, pages 284-295, XP009004570 ISSN: 0002-9297 cited in the application the whole document</p> <p>---</p>	1-20
A	<p>LA DU B N ET AL: "PROPOSED NOMENCLATURE FOR HUMAN BUTYRYLCHOLINESTERASE GENETIC VARIANTS IDENTIFIED BY DNA SEQUENCING" CELLULAR AND MOLECULAR NEUROBIOLOGY, NEW YORK, NY, US, vol. 11, no. 1, February 1991 (1991-02), pages 79-89, XP009000117 cited in the application the whole document</p> <p>-----</p>	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/41331**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-12 and 17-20 (all partly), 13-16 (completely)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12 and 17-20 (all partly), 13-16 (completely)

1.) The methods of claims 13-16 lack information as to the particular number and combination of markers to be employed, and the meaning of the vague and general term 'medical treatment course of action'. They also lack any information teaching the skilled person how to assign certain genetic markers to the particular 'course of action' to be chosen. Thus, these claims lack essential features and are unclear to such an extent that no meaningful search with respect to their subject matter was possible (Article 6 PCT).

2.) Present claims 1-12, 17-20 relate to a method defined by reference to a desirable characteristic, namely 'generating a genomic profile for use in selecting an operative course of action' (cf. e.g. claim 1), or selecting conditions for anesthesia (cf. e.g. claims 2-4).

The claims cover all methods having this characteristic, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for no such method whatsoever. This is because the only example of the application (page 43 ff.) merely enumerates several known markers which are characteristic for certain pathologies and complications in anesthesia. However, the description does not disclose how to combine or evaluate any combinations of markers in order to be able to decide which 'course of action' to take during an operation.

Consequently, the only method for which a search could be conducted was a method for the selection of conditions for anesthesia during a surgical procedure embracing a combination consisting of all genetic markers as specified in claim 12. Therefore, claims 1-20 have only been searched with respect to the combination of genetic markers mentioned in claim 12, and the only 'course of action' mentioned in the description, i.e., with respect to anesthesia (cf. description, Example 1, page 43 ff.).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter al Application No

PCT/US 01/41331

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5413907	A	09-05-1995	AT 116002 T 15-01-1995
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